CLAIMS

We claim:

1. A medical device comprising:

a stent structure having an outer surface and an inner surface that defines a lumen; and

a biologically active structure attached to the stent structure, the biologically active structure having a plurality of layers, a first layer of the plurality of layers having a first biologically active compound with a first biological activity, a second layer of the plurality of layers having a second biologically active compound having a second biological activity, and a third layer of the plurality of layers located between the first and second layers, wherein the third layer is substantially impermeable to the first biologically active compound and to the second biologically active compound.

2. The medical device of claim 1 wherein the second biological activity is substantially antagonistic to the first biological activity.

3. The medical device of claim 1 wherein the stent structure is comprised of one or more of the following materials: stainless steel, a nickel-titanium alloy, a cobalt-chromium alloy, a magnesium alloy, carbon, carbon fiber, or a polymer.

4. The medical device of claim 1 wherein the third layer is a membrane.

5. The medical device of claim 4 wherein the membrane is elastomeric, biocompatible, non-allergenic, and non-thrombotic.

6. The medical device of claim 4 wherein the membrane is comprised of polytetrafluoroethylene.

7. The medical device of claim 1 wherein the plurality of layers are elastomeric.

8. The medical device of claim 7 wherein the plurality of layers are biocompatible, non-allergenic, and non-thrombotic.

9. The medical device of claim 8 wherein each of the first, second and third layers of the plurality of layers is a polymer.

10. The medical device of claim 9 wherein elution kinetics of either the first biologically active compound or the second biologically active compound are predetermined based on the ratio of polymer to, respectively, either the first biologically active compound or the second biologically active compound.

11. The medical device of claim 9 wherein the polymer is selected from a plurality of polymers, the plurality of polymers comprising one or more of the following polymers, their respective derivatives and copolymers: poly(ethers), poly(ethylene oxide), poly(ethylene glycol), poly(tetramethylene oxide); vinyl polymers, poly(acrylates), poly(methacrylates) such as methyl, ethyl, other alkyl, hydroxyethyl methacrylate, acrylic acids, methacrylic acids, poly (vinyl alcohol), poly (vinyl pyrolidone), poly (vinyl acetate); poly(urethanes); cellulose and its derivatives s alkyl, hydroxyalkyl, ethers, esters, nitrocellulose, cellulose acetates; poly(siloxanes); plasticized nylon, plasticized soft nylon, natural rubber, silicone, medical grade silicone rubbers, ethylene-propylene rubber, silicone-carbonate copolymers, poly(olefins, poly(vinyl-olefins), poly(styrene), poly (halo-olefins), poly(isobutylene), polylactide, polylactide-co-glycolide, polydioxanone, thermoplastic elastomers, thermpoplastics, expanded PTFE, poly (vinyl-chloride), poly(isoprene), poly(isobutylene), poly(butadiene), polymalic acid, polyamino acids, polyacrylic acids, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohols, hydrophilic polyurethanes, albumin, collagen, gelatin, starch, cellulose, dextran, polymalic acid, polyamino acids and their co-polymers or lightly cross-linked forms, polysaccharides and their derivatives, sodium alginate, karaya gum, gelatin, guar gum, agar, align, carrageenans, pectin, locust bean gums, xanthan, starch-based gums, hydroxyalkyl and ethyl ethers of cellulose, sodium carboxymethylcellulose, poly(amides) such as poly(amino acids) and poly(peptides); poly(esters) such as poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid), and poly(caprolactone); poly(anhydrides); poly(orthoesters); poly(carbonates).

12. The medical device of claim 1 wherein the third layer is comprised of one or more of the following: ethylene vinyl acetate, latexes, urethanes, polysiloxanes, styrene-ethylene block copolymers, butylene-styrene block copolymers, silicone rubber, Silastic, and aliphatic polyesters, and mixtures and copolymers thereof.

13. The medical device of claim 1 wherein the biologically active structure is attached to the outer surface of the stent structure.

14. The medical device of claim 1 wherein the biologically active structure is attached to the inner surface of the stent structure.

15. The medical device of claim 1 wherein the biologically active structure is interleaved with the stent structure.

16. The medical device of claim 1 wherein the biologically active structure is attached to both the inner surface of the stent structure and the outer surface of the stent structure.

17. The medical device of claim 1 wherein the first layer and the second layer of the biologically active structure are each comprised of a plurality of sublayers.

18. The medical device of claim 17 wherein a first sublayer of the plurality of sublayers is a first polymer having either the first biologically active compound or the second biologically active compound, and wherein a second sublayer of the plurality of sublayers is a second polymer having a predetermined release rate, respectively, for the first biologically active compound or for the second biologically active compound.

19. The medical device of claim 17 wherein the first sublayer comprises a copolymer of ethylene-co-vinylacetate and polybutylmethacrylate and the second sublayer is polybutylmethacrylate.

20. The medical device of claim 1 wherein the first biological activity is a first pharmacological effect and the second biological activity is a second pharmacological effect, wherein the first pharmacological effect is opposing and adverse to the second pharmacological effect.

21. The medical device of claim 1 wherein the first biological activity is a first pharmacological effect and the second biological activity is a second pharmacological effect, wherein the first pharmacological effect interferes with the second pharmacological effect.

22. The medical device of claim 1 wherein the first biological activity is anti-proliferative.

23. The medical device of claim 1 wherein the first biological activity is anti-inflammatory.

24. The medical device of claim 1 wherein the first biological activity is either cytostatic or cytotoxic.

25. The medical device of claim 1 wherein the first biologically active compound is one or more of the following and analogues thereof: rapamycin, heparin, anti-thrombin compounds, prostaglandin inhibitors, platelet inhibitors, taxol, taxol derivatives, tacrolimus, tachrolimus-containing compounds, cytochalasin, paclitaxel, dexamethasone, a steroid compound, methotrexate, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, tyrosine kinase inhibitors, lidocaine, bupivacaine, ropivacaine.

26. The medical device of claim 1 wherein the second biologically active compound is a growth factor.

27. The medical device of claim 26 wherein the growth factor is one or more of the following: granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), CSF-1, G-CSF Ser.sup.17, M-CSF, c-mpl ligand (MGDF or TPO), erythropoietin (EPO),stem cell factor (SCF), interleukins 1 – 16 (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16), flt3 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, basic fibroblast growth factor, platelet-induced growth factor, transforming growth factor beta 1, acidic fibroblast growth factor, osteonectin, angiopoietin 1, angiopoietin 2, insulin-like growth factor, platelet-derived growth factor AA, platelet-derived growth factor BB, platelet-derived growth factor AB, endothelial PAS protein 1, thrombospondin, proliferin, Ephrin-A1, E-selectin, leptin, heparin, thyroxine, sphingosine 1-phosphate.

28. The medical device of claim 1 wherein the second biologically active compound is a cytokine.

29. The medical device of claim 28 wherein the cytokine is one or more of the following: a growth factor, beta interferon, gamma interferon, tumor necrosis factor.

30. The medical device of claim 1 wherein the second layer further comprises an antibody or antibody fragment.

31. The medical device of claim 30 wherein the antibody or antibody fragment has a binding affinity to one or more of the following: CD34 receptors, CD133 receptors, CDw90 receptors, CD117 receptors, HLA-DR, VEGFR-1, VEGFR-2, Muc-18 (CD146), CD130, stem cell antigen (Sca-1), stem cell factor 1 (SCF/c-Kit ligand), Tie-2, HAD-DR.

32. The medical device of claim 1 wherein the biologically active structure spans an entire length and entire circumference of the stent structure.

33. The medical device of claim 1 wherein the biologically active structure spans a partial length of the stent structure.

34. The medical device of claim 1 wherein the biologically active structure spans a partial circumference of the stent structure.

35. The medical device of claim 1 wherein a degree of impermeability of the third layer is selected based upon pharmacological sufficiency.

36. The medical device of claim 35 wherein the pharmacological sufficiency is determined by one or more of the following factors: selected purposes of the first second biologically active compound and the second biologically active compound; pharmacological effects of the first second biologically active compound and the second biologically active compound; medical treatment objectives; medical treatment durations; a rate of degradation or metabolism of the first second biologically active compound and the second biologically active compound and their active metabolites; a degree of acceptable elution without significantly adverse effects; a rate of bioresorption of the first layer or the second layer.

37. The medical device of claim 1 wherein, when the medical device is placed in an artery abutting vascular tissue, the first layer is capable of selectively releasing the first biologically active compound into the vascular tissue and the second layer is capable of selectively and independently releasing the second biologically active into an arterial lumen.

38. The medical device of claim 1 wherein the third layer is selectively impermeable.

39. A method of forming an implantable medical device, the implantable medical device capable of preventing restenosis and preventing thrombosis by aiding endothelialization of the implantable medical device, the method comprising:

providing a stent including an impermeable layer capable of substantially insulating a first biologically active compound from a second biologically active compound;

incorporating the first biologically active compound within a polymeric matrix on a first surface of the impermeable layer, wherein the first biologically active compound is capable of substantially preventing restenosis; and

incorporating a second biologically active compound within a polymeric matrix on a second surface of the impermeable layer, wherein the second biologically active compound is capable of substantially preventing thrombosis by substantially aiding endothelialization of the stent.

40. A method of treatment of myocardial tissue, capable of promoting the regeneration of myocardial cells, comprising the steps of:

inserting a stent into a first target site, the stent having a first biologically active compound having a first biological activity and having a second biologically active compound having a second, substantially antagonistic biologically activity, wherein the first biologically active compound is substantially insulated from the second biologically active compound;

delivering locally and selectively the first biologically active compound to the first target site; and

delivering the second biologically active compound via the bloodstream to a second target site.

41. The method of claim 40 wherein the second target site is myocardial tissue.

42. The method of claim 40 wherein the first biologically active compound is anti-proliferative and the second biologically active compound is a growth factor.

43. The method of claim 42 wherein the growth factor is substantially capable of promoting regeneration of myocardial tissue by aiding engraftment and differentiation of hematopoietic stem cells.

44. The method of claim 42 wherein the growth factor is substantially capable of promoting regeneration of myocardial tissue by aiding engraftment and differentiation of endothelial progenitor cells.

45. The method of claim 42 wherein the growth factor is one or more of the following: granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), CSF-1, G-CSF Ser.sup.17, M-CSF, c-mpl ligand (MGDF or TPO), erythropoietin (EPO),stem cell factor (SCF), interleukins 1 – 16 (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16), flt3 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, basic fibroblast growth factor, platelet-induced growth factor, transforming growth factor beta 1, acidic fibroblast growth factor, osteonectin, angiopoietin 1, angiopoietin 2, insulin-like growth factor, platelet-derived growth factor AA, platelet-derived growth factor BB, platelet-derived growth factor AB, endothelial PAS protein 1, thrombospondin, proliferin, Ephrin-A1, E-selectin, leptin, heparin, thyroxine, sphingosine 1-phosphate.

46. The method of claim 42 wherein the second biologically active compound further comprises an antibody or antibody fragment.

47. The method of claim 46 wherein the antibody or antibody fragment has a binding affinity to one or more of the following: CD34 receptors, CD133 receptors, CDw90 receptors, CD117 receptors, HLA-DR, VEGFR-1, VEGFR-2, Muc-18 (CD146), CD130, stem cell antigen (Sca-1), stem cell factor 1 (SCF/c-Kit ligand), Tie-2, HAD-DR.

48. The method of claim 40 wherein the second biologically active compound is a cytokine.

49. The method of claim 48 wherein the cytokine is one or more of the following: a growth factor, beta interferon, gamma interferon, tumor necrosis factor.

50. A medical device comprising

a stent structure having an outer surface and an inner surface that defines a lumen; and

a biologically active structure attached to the stent structure, the biologically active structure having a plurality of layers, a first layer of the plurality of layers having a first biologically active compound with a first biological activity, a second layer of the plurality of layers having a second biologically active compound having a second biological activity, and a third layer of the plurality of layers located between the first and second layers, wherein the second biological activity is substantially antagonistic to the first biological activity.

51. The medical device of claim 50 wherein the third layer is substantially impermeable to the first biologically active compound and to the second biologically active compound.

52. The medical device of claim 51 wherein the third layer is a biocompatible, non-allergenic, and non-thrombotic membrane comprised of polytetrafluoroethylene.

53. The medical device of claim 50 wherein the third layer is selectively impermeable to the first biologically active compound and to the second biologically active compound.

54. The medical device of claim 50 wherein the plurality of layers are one or more elastomeric, biocompatible, non-allergenic, and non-thrombotic polymers.

55. The medical device of claim 50 wherein elution kinetics of either the first biologically active compound or the second biologically active compound are predetermined based on the ratio of polymer to, respectively, either the first biologically active compound or the second biologically active compound.

56. The medical device of claim 50 wherein the first layer and the second layer of the biologically active structure are each comprised of a plurality of sublayers.

57. The medical device of claim 56 wherein a first sublayer of the plurality of sublayers is a first polymer having either the first biologically active compound or the second biologically active compound, and wherein a second sublayer of the plurality of sublayers is a second polymer having a predetermined release rate, respectively, for the first biologically active compound or for the second biologically active compound.

58. The medical device of claim 56 wherein the first sublayer comprises a copolymer of ethylene-co-vinylacetate and polybutylmethacrylate and the second sublayer is polybutylmethacrylate.

59. The medical device of claim 50 wherein the first biological activity is anti-proliferative and anti-inflammatory.

60. The medical device of claim 50 wherein the first biological activity is either cytostatic or cytotoxic.

61. The medical device of claim 50 wherein the first biologically active compound is one or more of the following: rapamycin, heparin, anti-thrombin compounds, prostaglandin inhibitors, platelet inhibitors, taxol, taxol derivatives, tacrolimus, tachrolimus-containing compounds, cytochalasin, paclitaxel, dexamethasone, a steroid compound, methotrexate, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, tyrosine kinase inhibitors, lidocaine, bupivacaine, ropivacaine..

62. The medical device of claim 50 wherein the second biologically active compound is a growth factor.

63. The medical device of claim 62 wherein the growth factor is one or more of the following: granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), CSF-1, G-CSF Ser.sup.17, M-CSF, c-mpl ligand (MGDF or TPO), erythropoietin (EPO),stem cell factor (SCF), interleukins 1 – 16 (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16), flt3 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, basic fibroblast growth factor, platelet-induced growth factor, transforming growth factor beta 1, acidic fibroblast growth factor, osteonectin, angiopoietin 1, angiopoietin 2, insulin-like growth factor, platelet-derived growth factor AA, platelet-derived growth factor BB, platelet-derived growth factor AB, endothelial PAS protein 1, thrombospondin, proliferin, Ephrin-A1, E-selectin, leptin, heparin, thyroxine, sphingosine 1-phosphate.

64. The medical device of claim 50 wherein the second layer further comprises an antibody or antibody fragment. having a binding affinity to CD34 receptors of hematopoietic stem cells.

65. The medical device of claim 64 wherein the antibody or antibody fragment has a binding affinity to one or more of the following: CD34 receptors, CD133 receptors, CDw90 receptors, CD117 receptors, HLA-DR, VEGFR-1, VEGFR-2, Muc-18 (CD146), CD130, stem cell antigen (Sca-1), stem cell factor 1 (SCF/c-Kit ligand), Tie-2, HAD-DR.

66. The medical device of claim 50 wherein the second biologically active compound is a cytokine.

67. The medical device of claim 66 wherein the cytokine is one or more of the following: a growth factor, beta interferon, gamma interferon, tumor necrosis factor.

68. A medical device for drug delivery, comprising

a stent structure having an outer surface and an inner surface that defines a lumen; and

a biologically active structure attached to the stent structure, the biologically active structure having a plurality of layers, a first layer of the plurality of layers having a biologically active compound with a biological activity, and a second layer of the plurality of layers being substantially impermeable to the biologically active compound.

69. The medical device of claim 68 wherein the second layer is attached to the outer surface of the stent structure, or wherein the first layer is attached to the inner surface of the stent structure, or wherein the first layer is attached to the outer surface of the stent structure and the second layer is attached to the inner surface of the stent structure.

70. The medical device of claim 69 wherein the biological activity is anti-proliferative and anti-inflammatory.

71. The medical device of claim 69 wherein the first biological activity is either cytostatic or cytotoxic.

72. The medical device of claim 69 wherein the first biologically active compound is one or more of the following: rapamycin, heparin, anti-thrombin compounds, prostaglandin inhibitors, platelet inhibitors, taxol, taxol derivatives, tacrolimus, tachrolimus-containing compounds, cytochalasin, paclitaxel, dexamethasone, a steroid compound, methotrexate, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, tyrosine kinase inhibitors, lidocaine, bupivacaine, ropivacaine..

73. The medical device of claim 68 wherein the second layer is attached to the inner surface of the stent structure, or wherein the first layer is attached to the outer surface of the stent structure, or wherein the first layer is attached to the inner surface of the stent structure and the second layer is attached to the outer surface of the stent structure..

74. The medical device of claim 73 wherein the biologically active compound is a growth factor.

75. The medical device of claim 73 wherein the growth factor is one or more of the following: granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), CSF-1, G-CSF Ser.sup.17, M-CSF, c-mpl ligand (MGDF or TPO), erythropoietin (EPO),stem cell factor (SCF), interleukins 1 – 16 (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16), flt3 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, basic fibroblast growth factor, platelet-induced growth factor, transforming growth factor beta 1, acidic fibroblast growth factor, osteonectin, angiopoietin 1, angiopoietin 2, insulin-like growth factor, platelet-derived growth factor AA, platelet-derived growth factor BB, platelet-derived growth factor AB, endothelial PAS protein 1, thrombospondin, proliferin, Ephrin-A1, E-selectin, leptin, heparin, thyroxine, and sphingosine 1-phosphate.

76. The medical device of claim 73 wherein the biologically active compound is an antibody or antibody fragment.

77. The medical device of claim 76 wherein the antibody or antibody fragment has a binding affinity to one or more of the following: CD34 receptors, CD133 receptors, CDw90 receptors, CD117 receptors, HLA-DR, VEGFR-1, VEGFR-2, Muc-18 (CD146), CD130, stem cell antigen (Sca-1), stem cell factor 1 (SCF/c-Kit ligand), Tie-2, HAD-DR.

78. The medical device of claim 73 wherein the biologically active compound is a cytokine.

79. The medical device of claim 78 wherein the cytokine is one or more of the following: a growth factor, beta interferon, gamma interferon, tumor necrosis factor.

80. The medical device of claim 68 wherein the plurality of layers are elastomeric, biocompatible, non-allergenic, and non-thrombotic polymer.

81. The medical device of claim 68 wherein the first layer of the biologically active structure is comprised of a plurality of sublayers.

82. The medical device of claim 81 wherein a first sublayer of the plurality of sublayers is a first polymer having the biologically active compound, and wherein a second sublayer of the plurality of sublayers is a second polymer having a predetermined release rate for the biologically active compound.

83. The medical device of claim 82 wherein the first sublayer comprises a copolymer of ethylene-co-vinylacetate and polybutylmethacrylate and the second sublayer is polybutylmethacrylate.

84. A medical device for drug delivery, comprising

a stent structure having an outer surface and an inner surface that defines a lumen; and

a biologically active structure attached to the stent structure, the biologically active structure having a plurality of layers, a first layer of the plurality of layers having a growth factor, and a second layer of the plurality of layers being substantially impermeable to the growth factor.

85. The medical device of claim 84 wherein the growth factor is one or more of the following: granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), CSF-1, G-CSF Ser.sup.17, M-CSF, c-mpl ligand (MGDF or TPO), erythropoietin (EPO),stem cell factor (SCF), interleukins 1 – 16 (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16), flt3 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, basic fibroblast growth factor, platelet-induced growth factor, transforming growth factor beta 1, acidic fibroblast growth factor, osteonectin, angiopoietin 1, angiopoietin 2, insulin-like growth factor, platelet-derived growth factor AA, platelet-derived growth factor BB, platelet-derived growth factor AB, endothelial PAS protein 1, thrombospondin, proliferin, Ephrin-A1, E-selectin, leptin, heparin, thyroxine, sphingosine 1-phosphate.

86. The medical device of claim 84 wherein the first layer further comprises an antibody or antibody fragment having a binding affinity to one or more of the following: CD34 receptors, CD133 receptors, CDw90 receptors, CD117 receptors, HLA-DR, VEGFR-1, VEGFR-2, Muc-18 (CD146), CD130, stem cell antigen (Sca-1), stem cell factor 1 (SCF/c-Kit ligand), Tie-2 and HAD-DR.

87. The medical device of claim 84 wherein the first layer further comprises a one or more of the following cytokines: beta interferon, gamma interferon, and tumor necrosis factor.